EXHIBIT-1 46

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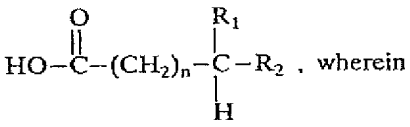
(54) NOVEL ESTERS OF TESTOSTERONE AND 5α-DIHYDRO-TESTOSTERONE

(71) We, AKZO N.V., a Dutch Body Corporate, of Ijssellaan 82, Arnhem, The Netherlands, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:-

The invention relates to novel 17β-esters of testosterone and 5α-dihydrotestosterone. Esters of testosterone (17β-hydroxy-Δ^4-androsten-3-one) and 5α-dihydrostestosterone (17β-hydroxy-5αH-androstan-3-one) (hereunder further indicated by the abbreviations T and DHT, respectively) are known. In medicine, these androgenic substances are employed, for instance, in men with an insufficiency of endogenous androgens. Esters of T or DHT are usually administered parenterally, i.e. injected while dissolved or suspended in a suitable liquid carrier. T and DHT show only very little activity when administered orally. It is known that the oral activity can be enhanced by administering T or DHT in the presence of an oil, especially when T and DHT are taken in the form of their esters derived from aliphatic carboxylic acids, such as the decanoate and undecanoate.

Surprisingly, it has now been found that novel T- and DHT-esters, derived from certain branched chain aliphatic monocarboxylic acids with 8-16 carbon atoms possess very interesting androgenic activities, in particular on oral application in the presence of a pharmaceutically acceptable lipoid.

The present invention therefore relates to 17β-esters of T and DHT derived from an aliphatic monocarboxylic acid having the formula:



, wherein

n is O or 1; R_1 is alkyl (1–5 C); R_2 is alkyl (3–10 C), with the proviso that R_2 is not alkyl (3–6 C) when R_1 = alkyl (1–2 C), or R_2 is an cyclo-aliphatic group having 6–10 C-atoms, said cyclo-aliphatic group containing a 6-membered ring; or $R_1 + R_2$ form together with the C-atom to which they are attached a cyclo-alkyl group having 7–12 C-atoms, preferably 8–10 C-atoms, which group may be substituted by alkyl (1–3 C); with the proviso that the total number of C-atoms in the ester group is in the range of 8–16 C-atoms, preferably 8–12 C-atoms.

R_2 is preferably equal to R_1 when R_1 = alkyl (3–5C) and is preferably alkyl (7–8 C) when R_1 = alkyl (1–2 C).

The novel esters can be prepared according to methods known in the art for example by reacting T or DHT with the said monocarboxylic acid or a functional derivative thereof, such as the acid halide (acid chloride or acid bromide) or the acid anhydride.

Reaction of T or DHT with the monocarboxylic acid as such can be performed for example by melting the two reactants together or by reacting the two reactants in a solvent, such as acetonitrile, with the aid of a water binding agent, such as dicyclohexylcarbodiimide.

Reaction of T or DHT with the acid halide, such as the chloride, is usually performed in a solvent, such as acetone, hexane, toluene or pyridine, and in the presence of a base, such as

pyridine or dimethylaniline.

Reaction of T or DHT with the acid anhydride is usually performed in a solvent such as hexane, pentane or toluene, and in the presence of either a base, such as pyridine, or an acid catalyst, such as p-toluene sulphonic acid, dinitrobenzene sulphonic acid or sulfosalicylic acid.

Specific examples of the branched chain aliphatic monocarboxylic acids, which can be used for preparing the novel esters according to the invention, are 2-methyl-decanoic acid, 3-methyl-decanoic acid, 2-methyl-3-cyclohexyl-propionic acid, 2-cyclohexyl-butyric acid, cycloheptyl-acetic acid, cyclo-octyl-acetic acid, cyclo-octane carboxylic acid, cyclodecane carboxylic acid, cyclo-dodecane carboxylic acid, 3-butyl-heptanoic acid, 2-propyl-pentanoic acid and 2-butyl-hexanoic acid.

As mentioned already, the anhydride or the acid chlorides or bromides of these acids can also be used.

The esters according to the invention can be administered in the usual dosage form for enteral and parenteral administration, such as tablets, powders, capsules, grains, pills, boli, dragees, granulates, microcapsules, suppositories, solutions and dispersions.

The novel T- and DHT-esters are particularly useful as androgenic substances for oral administration and are particularly effective when administered orally in the presence of a lipoid substance, preferably a pharmaceutically acceptable non-steroidal lipoid.

By pharmaceutically acceptable non-steroidal lipoids are meant plant and animal oils and fats consisting of the mono-, di- and tri-glycerides of various fatty acids or containing these as main constituents; fatty acid esters of alcohols; higher aliphatic alcohols (> 6 C-atoms); saturated and unsaturated fatty acids; the commercially available synthetic and semi-sunthetic mono-, di-, and tri-glyceride oils and glycerol ethers; certain types of wax and mixtures of two or more of the above-noted substances. The lipoid substance may be liquid at normal temperature, that is, at a temperature in the range of about 10°C to about 35°C. The T- or DHT-ester is then dissolved in the lipoid substance and the solution is incorporated into a preparation or, as the case may be, converted into a pharmaceutical form. At normal temperature a part of the ester may be present in the liquid lipoid as a suspension, in which case the quantities of ester and lipoid substance are mutually adjusted in such a way that at body temperature the ester is completely dissolved in the lipoid substance.

Examples of lipoid substances which may be used in the preparation according to the invention are: arachis oil, castor oil, sesame oil, linseed oil, soya bean oil, sunflower seed oil, olive oil, fish liver oil, ethyl oleate, oleyl oleate, glyceryl trioleate, glyceryl diolate, glyceryl monooleate, cetyl alcohol, stearyl alcohol, capric acid, indecenoic acid, undecanoic acid, lauric acid, oleic acid, synthetic glycerides of saturated fatty acids with 8 to 10 or 12 carbon atoms such as the commercial products Syndermin (Registered Trade Mark) GTC and Miglyol (Registered Trade Mark) 812, polyoxyethylene derivatives of glycerol such as the commercial product Labrafil (Registered Trade Mark) 1944, bee's wax and mixtures of two or more of these substances.

The combination of a novel T- or DHT-ester and a lipoid, when liquid or semi-liquid, may also be processed to solid oral formulations such as pills or tablets. For that purpose the oily solution of the steroid-ester is, for example, absorbed on calcium phosphate, lactose or cellulose derivatives and then processed to tablets or pills in the usual way. Combinations of T- or DHT-esters with lipoids, such as glycerylmono-oleate or caprinic acid, which are solid or semi-solid at room temperature, but are liquid at body temperature, may be granulated and processed to coated pills or tablets.

The enteral and parenteral dosage forms may contain one or more of the usual excipients, for example benzyl alcohol to increase the solubility of the active substance in the oil component, water, thickening agents such as gelatine or agar, polyethylene glycols, lactose, starch, talc or magnesium stearate. Other agents, such as preservatives, emulsifying agents, stabilizing agents, wetting agents, flavours, dyes, fillers, binding agents and/or encapsulating agents may optionally also be present.

As already noted above, the T- or DHT-esters according to the invention can be administered dissolved in lipoid substances liquid at normal temperature.

The most suitable oral administration form for this liquid form of the preparation according to the invention is the soft gelatine capsule or microcapsule. In accordance with a method usual in the technique, the oily solution containing the active component and optionally other ingredients is encapsulated in soft gelatine capsules or microcapsules with the desired dimensions and containing the desired amount(s) of active substances. The microcapsules can also be processed to tablets or pills according to well-known pharmaceutical formulation methods.

The androgenic ester concentration in the dosage forms containing a lipoid can vary within considerable limits, on the understanding that the amount of T- or DHT-ester by

weight does not exceed the amount of lipoid substance by weight or in other words the androgenic ester concentration in the preparation is 50% by weight or less and is usually in the range of 1-40% by weight.

As indicated above, the amount of lipoid by weight in the preparation according to the invention is equal to or higher than the amount of androgenic ester by weight. Depending on the other constituents present in the preparation (excipients, capsule shell, coating) the amount of lipoid substance per dosage unit will vary from 25 to 95% by weight and is usually in the range of 40-80% by weight. The amount of androgenic ester per dosage unit, for example a capsule or a tablet, may also vary within wide limits, for example from 0.5 mg to 400 mg, and is preferably between 1 mg and 200 mg.

The useful androgenic properties of the novel T- and DHT-esters can be demonstrated for example by experiments in castrated rats (Hershberger test), wherein the increase in weight of the seminal vesicles and the ventral prostate is determined after having orally dosed the active substance for seven days once or twice a day.

In this way it turned out in such an experiment that with a daily dose in the range of 2 × 0.5 to 2 × 2 mg in arachis oil, the androgenic acitivity of for example testosterone 3-cyclohexylbutyrate, testosterone 2-methyl-3-cyclohexylpropionate, testosterone 2-methyl-decanoate and testosterone cyclo-octyl-acetate was determined to be 2 to 5 times greater than that of testosterone decanoate, an unbranched ester. Similar results were also found with DHT-esters.

In clinical trials with novel esters according to the invention, wherein a daily dose of T-ester in the range from 20 to 100 mg was administered, a considerable increase of the plasma-T level was found both in men with a normal plasma-T level and in men with a lower level resulting from a decreased production of endogenous T.

A daily oral dose of 25 mg testosterone cyclo-octyl-acetate in 0.24 ml oleic acid in a soft gelatine capsule for three months to a hypogonadal man gave an increase of the plasma-T level to normal value.

The present invention will now be illustrated with the following Examples.

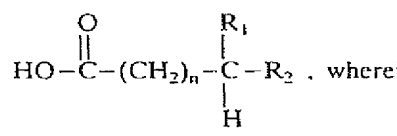
Examples

To a solution of 2 g testosterone in a mixture of 8 ml pyridine and 8 ml acetone, cooled to −10°C, was added dropwise in a nitrogen atmosphere a solution of 4 ml 2-methyl-decanoyl-chloride in 12 ml acetone. The mixture was stirred for 16 hours at 0°C, whereafter 4 ml pyridine and 8 ml water were added to the mixture. The mixture was stirred for 1 hour at 0°C and 2 hours at 45°C and then poured out in 200 ml ice-water. Extraction with diethylether, neutralisation of the extracts, evaporation of the diethyl-ether and chromatography of the residue on silicagel with toluene/ethylacetate 8/2 gave 3.0 g testosterone 2-methyl-decanoate in the form of an oil with $[\alpha]_D^{20} = + 77.0°$ (in methylenechloride) and ϵ_{mol} 16.800 (λ_{max} 240 mμ).

In a similar manner the following 17ß-esters were prepared:
T−3-methyl-decanoate, oil with $[\alpha]_D^{20} = + 80°$;
T−2-methyl-3-cyclohexyl-propionate, m.p. 133-136°C, $[\alpha]_D^{20} = + 68°$;
T−3-cyclohexyl-butyrate, m.p. 82-88°C, $[\alpha]_D^{20} = + 80.7°$;
T-cyclododecane carboxylate, m.p. 116-119°C, $[\alpha]_D^{20} = + 84°$;
DHT−2-methyl-decanoate, m.p. 86-87°C, $[\alpha]_D^{20} = + 25°$;
T-cyclo-octyl-acetate, m.p. 82-83°C, $[\alpha]_D^{20} = + 84°$;
T−2-propyl-pentanoate, m.p. 83-85°C, $[\alpha]_D^{20} = + 84°$;
T−3-butyl-heptanoate, oil with $[\alpha]_D^{20} = + 77.0°$;
T−2-butyl-hexanoate, oil with $[\alpha]_D^{20} = + 74.2°$;
($[\alpha]_D^{20}$ has been determined in methylenechloride).

WHAT WE CLAIM IS:-

1. 17ß-esters of testosterone and 5α-dihydro-testosterone derived from an aliphatic monocarboxylic acid having 8−16 carbon atoms and having the formula:



, wherein

n = 0 or 1;
R_1 = alkyl (1−5 C);
R_2 = alkyl (3−10 C) with the proviso that R_2 is not alkyl (3−6 C), when R_1 = alkyl (1−2 C), or R_2 = a cyclo-aliphatic group having 6−10 C-atoms, said cyclo-aliphatic group containing a 6-membered ring; or

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$R_1 + R_2$ form together with the C-atom to which they are attached a cyclo-alkyl group having 7-12 C-atoms, which group may be substituted by alkyl (1–3 C).

2. Esters according to claim 1, wherein $R_1 = R_2$, when R_1 = alkyl (3–5 C).

3. Esters according to claim 1, wherein R_2 = alkyl (7–8 C), when R_1 = alkyl (1–2 C).

4. Esters according to claim 1, wherein R_2 = cyclohexyl and R_1 = methyl.

5. Esters according to claim 1, wherein $R_1 + R_2$ together with the C-atom to which they are attached is cyclo-octyl.

6. Esters according to claim 1–5, wherein the total number of C-atoms in the aliphatic monocarboxylic acid residue is in the range of 8 to 12.

7. An ester accordinvg to claim 1 and substantially as described in any preceding Example.

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